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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/89492 A1

(54) Title: NOVEL COMPOSITION

(57) Abstract: The invention relates to novel pharmaceutical compositions useful in the treatment of respiratory disorders such as asthma, rhinitis and chronic obstructive pulmonary disease (COPD).

Novel composition

Field of the invention

The present invention relates to a stable powder formulation comprising formoterol or enantiomers of formoterol, a glucocorticosteroid and a carrier or diluent for use in the treatment of inflammatory conditions/disorders, especially respiratory diseases such as asthma, COPD and rhinitis.

Background of the invention

Stability is one of the most important factors which determines whether a compound or a mixture of compounds can be developed into a therapeutically useful pharmaceutical product. When mixing different ingredients in a pharmaceutical formulation there exists the possibility of interactions taking place between the components. In addition, each component may have different degradation characteristics.

Formoterol is a highly potent and selective β2-agonist with a long duration of action when inhaled. Compared to other β-adrenergic compounds it has a unique chemical structure with a formamido group substituted on the benzene ring. It has two asymmetric carbon atoms in the molecule making four stereoisomers possible. Most studies, clinical and preclinical, appear to have been performed with the fumarate (as dihydrate) of the enantiomeric mixture designed R;R + S;S. The R;R enantiomer is the most potent of the four enantiomers.

The stability profile of the drug formoterol (mainly as fumarate dihydrate) has been evaluated by investigating the influence of variables such as storage time, temperature, relative humidity, light and pH on the content of formoterol and determining the amount of chromatographic impurities. Formoterol (as fumarate dihydrate) has been demonstrated to be stable under long-term storage even at high temperatures and high relative humidities.

However, the chemical structure of formoterol makes the molecule prone to chemical degradation when in contact with e.g. a reactive species like an aldehyde or under stress conditions e.g. a milling process.

Potent drugs for administration by inhalation are generally formulated in association with carriers/diluents such as lactose to facilitate accurate dosing from an inhaler. These formulations have generally consisted of coarse particles of a carrier together with fine particles of the drug(s), optionally together with small particles of carrier/diluent, which combination is generally known as an ordered mixture. An alternative to such a formulation is to agglomerate the small particles of the drug(s) and the carrier/diluent to agglomerates.

Formoterol (as fumarate dihydrate) as well as a carbohydrate such as lactose (preferably as the monohydrate) are very stable compounds individually, but degradation products are formed when the two compounds are mixed. A mixture of formoterol fumarate dihydrate and lactose monohydrate can be regarded as a three component system composed of formoterol fumarate, lactose and water. By sorption of water a saturated aqueous lactose solution is formed at the surface of the powder mixture. A certain amount of formoterol fumarate dissolves in this aqueous solution and is thereby susceptible to degradation. Therefore, the relative humidity, as well as the storage temperature, will influence the stability of the powder mixture.

When adding a third ingredient in the mixture the formation of degradation products would be expected to be higher due to the complexity and the possibility for many degradation processes. It would therefore be desirable to develop a formulation with good stability in spite of the complex mixture of compounds having reactive chemical functions such as an amine (formoterol), formamide (formoterol), carbohydrate (e.g. lactose) and a keto function (glucocorticosteroid). The presence of hydrates (formoterol fumarate dihydrate, lactose monohydrate) will make it even more complex.

Description of the invention

In accordance with the present invention, there is provided a pharmaceutical composition in the solid state comprising, in admixture, a first active ingredient which is micronised formoterol or an enantiomer thereof, a second active ingredient which is a micronised glucocorticosteroid and a carrier or diluent, the composition having a high storage stability.

By the term "high storage stability" is meant that the decomposition of formoterol in the formulation will be less than 10 % when stored in open dishes at 40°C and 75 % relative humidity for 6 months when the content of formoterol is less than about 1.0% (w/w), preferably less than 0.8 % (w/w) and most preferably less than about 0.6 % (w/w) in the formulation or, when stored in a dry powder device, a decomposition of less than about 2.5 % under the same conditions.

The formulations having the desired stability are prepared using a novel process which involves:

1. preparing a mixture of micronised first active ingredient and micronised carrier/diluent
2. optionally adding further micronised carrier/diluent to the mixture
3. addition and mixing of pre-micronised hydrophobic second active ingredient, the second active ingredient being optionally pre-mixed with micronised carrier/diluent, and
4. either subjecting the mixture to agglomeration and spheronisation, or adding coarse carrier/diluent.

The first active ingredient and carrier/diluent can be prepared according to step 1 by micronising the two components together or each can be micronised individually and then combined to give a micronised mixture. Preferably the two components are mixed together and then micronised.

Preferably at step 3 the pre-micronised hydrophobic second active ingredient is added alone, ie in the absence of further micronised carrier/diluent.

Preferably step 4 involves subjecting the mixture to agglomeration and spheronisation.

By "micronised" is meant milling to give the a desired particle size or obtaining a desired particle size by any other means for producing small particles such as direct precipitation.

Optionally the mixture/ingredients can be conditioned at any suitable stage of the process, such as between steps 1 and 2, and/or the further pre-micronised carrier/diluent can be conditioned prior to addition at step 2, and/or the further pre-micronised carrier/diluent can be conditioned prior to addition at step 3, and/or the mixture can be conditioned between the agglomeration and spheronisation in step 4.

Conditioning can be carried out according to the procedures described in WO 95/05805 or by selecting the process parameters such as relative humidity in such a way that the final product when submitted to water vapour gives off heat of less than 1.2 joules per gram for the particles having a mean particle size of less than 10 μm as described and measured in US 5.874,063.

The invention therefore provides a pharmaceutical formulation in the solid state comprising, in admixture, a first active ingredient which is micronised formoterol or an enantiomer thereof, a second active ingredient which is a micronised glucocorticosteroid and a carrier/diluent and having a high storage stability characterised in that the formulation is prepared by micronisation of the first active ingredient and carrier/diluent, optionally followed by mixing pre-micronised coarser carrier/diluent, mixing with micronised hydrophobic second active ingredient., and finally either subjecting the mixture to agglomeration and spheronisation or adding coarse carrier/diluent.

The formoterol can be in the form of a mixture of enantiomers. Preferably the formoterol is in the form of a single enantiomer, preferably the R;R enantiomer. The formoterol can be in the form of the free base, salt or solvate, or a solvate of a salt, preferably the formoterol is in the form of its fumarate dihydrate salt. Other suitable physiologically salts include chloride, bromide, sulphate, phosphate, maleate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, benzenesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricaballate, hydroxynapaphthalenecarboxylate or oleate.

Preferably the second active ingredient is a micronised glucocorticosteroid such as budesonide, fluticasone propionate, mometasone furoate, ciclesonide and epimers, esters, salts and solvates of these compounds. More preferably the second active ingredient is budesonide or an epimer thereof, most preferably the 22R-epimer of budesonide.

Preferably the carrier is a carbohydrate having a high storage stability, preferably a reducing carbohydrate such as lactose, glucose, galactose, mannose, xylose, maltose, cellobiose, mellibiose, maltotriose (e.g. as monohydrate). More preferably the carrier is lactose.

As used herein the term micronised carrier/diluent refers to carrier/diluent having a mean particle size of less than about 25 μm, preferably less than about 10 μm, more preferable less than about 5 μm. The micronised carrier can be produced using processes known in the art such as micronisation or direct precipitation. The term coarse carrier/diluent refers to carrier/diluent having a mean particle size of greater than about 25 μm.

As used herein the term micronised first active ingredient or micronised second active ingredient means active ingredient having a mean particle size of less than about 10 μm, preferably less than about 5 μm.

The pharmaceutical compositions according to the invention can be used for the treatment or prophylaxis of a respiratory disorder, in particular the treatment or prophylaxis of asthma, rhinitis or COPD.

In a further aspect the invention provides a method of treating a respiratory disorder, in particular asthma, rhinitis or COPD, in a mammal which comprises administering to a patient a pharmaceutical composition as herein defined.

The compositions of the invention can be inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler e.g. multidose reservoir systems from AstraZeneca (Turbuhaler®) or Schering-Plough or from a dry powder inhaler utilizing gelatine, plastic or other capsules, cartridges or blister packs. Doses will be dependent on the severity of the disease and the type of patient.

The process of the invention is shown schematically in Figure 3.

Experimental section

The invention is illustrated by the following examples which are not intended to limit the scope of the application. In the examples micronisation is carried out such that the particle size range for each of the active components is suitable for administration by inhalation. The determination of the formoterol degradation products was performed by reversed phase liquid chromatography, on a two column system using LiChrospher 60 RP-select B. 5 μm particles with octylsilane as stationary phase. UV-detector at 214 nm. Evaluation was done as area-% since the degradation products were not fully known.

Example 1

The following example is a reference example in which the formulation is prepared in a conventional manner.

Formoterol fumarate dihydrate (26 g) and lactose monohydrate (4.974 kg) are mixed for one or two hours in a tumbling mixer. This mixture was micronised in a spiral jet mill in order to attain a particle size suitable for inhalation. Micronisation of substances into the low micron range (1-5 μm) may induce disturbances in the crystallinity of the substance. Amorphous areas are introduced, especially at the surfaces of the micronised substance. This morphological change of the substances will increase the sensitivity to humidity and thereby being an potential implement to stability problems. The crystal structure of the substance mixture was restored in a controlled way according to US 5.874.063 or US 5.709.884.

To improve the flowability of the cohesive powder it was spheronised to agglomerates at room temperature at a controlled relative humidity of less than 50 %.

Stability data of a formoterol fumarate dihydrate (5 mg/g)/lactose monohydrate (995 mg/g) micronised mixture and stored in open dishes at 40°C and 75 % relative humidity for 6 months. Results see figure 1 (A).

Example 2.

The following example is a reference example in which the formulation is prepared in a conventional manner.

The micronised and spheronised formoterol fumarate dihydrate/lactose monohydrate formulation according to example 1 was filled in the powder device Turbuhaler® (AstraZeneca) and stored for 6 months at 40°C and 75 % relative humidity. Results see figure 2 (A).

Example 3.

Formoterol fumarate dihydrate (0.2 kg) and lactose monohydrate (34 kg) are mixed for one or two hours in a tumbling mixer. This mixture was micronised in a spiral jet mill in order to attain a particle size suitable for inhalation. The crystal structure was restored in a controlled way according to US 5.874.063 or US 5.709.884. This conditioned product is mixed with micronised budesonide (3 kg) for thirty to sixty minutes in a tumbling mixer. As a second mixing step the powder was fed to a modified spiral jet mill, operating at a very low milling pressure and a high flow of nitrogen. This will break up agglomerates without causing a further size reduction of the particles (and thereby creating amorphous areas and as a consequence loss of stability) while improving the homogeneous distribution of budesonide in the powder.
To improve the flowability of the cohesive powder it was spheronised to agglomerates at room temperature at a controlled relative humidity of less than 50 %.

Stability data of a formoterol fumarate dihydrate (5 mg/g)/budesonide (90 mg/g)/lactose monohydrate (905 mg/g) micronised mixture and stored in open dishes at 40°C and 75 % relative humidity for 6 months. Results see figure 1(B).

Example 4.

The micronised and spheronised formoterol fumarate dihydrate (5 mg/g)/budesonide (90 mg/g)/lactose monohydrate (905 mg/g) according to example 3 was filled in the dry powder device Turbuhaler® (AstraZeneca) and stored for 6 months at 40°C and 75 % relative humidity. Results see figure 2 (B).

Claims.

1. A pharmaceutical composition comprising, in admixture, a first active ingredient which is micronised formoterol optionally in the form of a salt or solvate or a solvate of a salt, a second active ingredient which is a micronised glucocorticosteroid and a pharmaceutically acceptable carrier/diluent, the composition having a high storage stability.

2. A pharmaceutical composition according to claim 1 in which formoterol is in the form of its fumarate dihydrate salt

3. A pharmaceutical composition according to claim 1 or 2 in which the formoterol is in the form of the single R,R-enantiomer.

4. A pharmaceutical composition according to any one of claims 1 to 3 in which the second active ingredient is budesonide.

5. A pharmaceutical composition according to any one of claims 1 to 3 in which the second active ingredient is the 22R-epimer of budesonide.

6. A pharmaceutical composition according to any one of claims 1 to 5 in which the carrier/diluent is lactose.

7. A pharmaceutical composition according to any one of claims 1 to 6 in which the particle size of the active ingredients is less than about 10 μm.

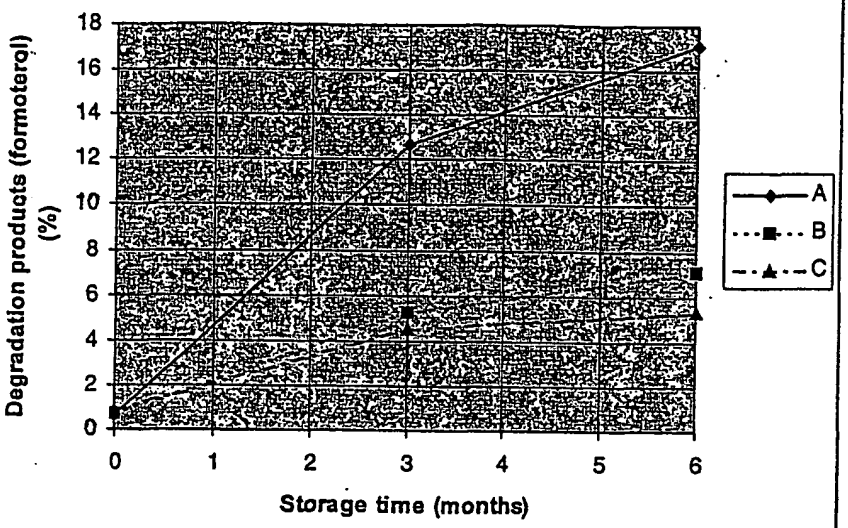
8. A pharmaceutical composition according to any one of claims 1 to 7 for use for the treatment or prophylaxis of a respiratory disorder.

9. A pharmaceutical composition according to any one of claims 1 to 7 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.

10. A method of treating a respiratory disorder in a mammal which comprises administering to a patient a pharmaceutical composition according to any one of claims 1 to 7.

Stability data for formoterol / lactose vs formoterol / budesonide / lactose (open dishes)

Figure 1



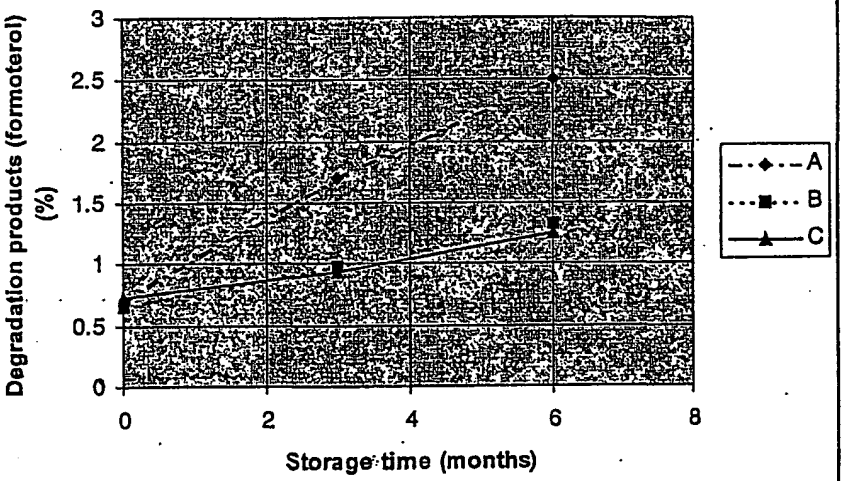
A= formoterol fumarate dihydrate (0.5%) / lactose monohydrate (99,5%) according to example 1

B= formoterol fumarate dihydrate (0.5%) / budesonide (9%) / lactose monohydrate (90.5%)

C= formoterol fumarate dihydrate (0.5%) / budesonide (18%) / lactose monohydrate (81.5%)

Stability data for formoterol / lactose vs formoterol / budesonide / lactose (Turbuhaler)

Figure 2

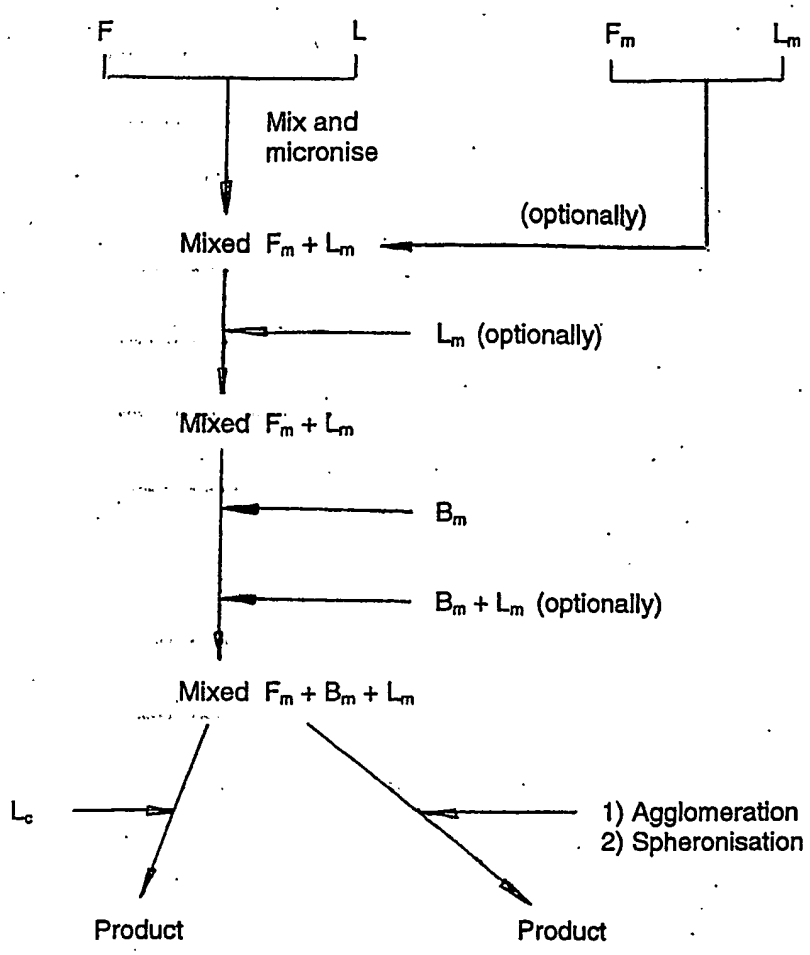


A= formoterol fumarate dihydrate (0.5%) / lactose monohydrate (99,5%); 4.5µg formoterol fumarate dihydrate / dose according to example 2.

B= formoterol fumarate dihydrate (0.5%) / budesonide (9%) / lactose monohydrate (90.5%); 4.5µg formoterol fumarate dihydrate / 80 µg budesonide/dose

C= formoterol fumarate dihydrate (0.5%) / budesonide (18%) / lactose monohydrate (81.5%); 4.5µg formoterol fumarate dihydrate / 160 µg budesonide/dose

Figure 3



L = carrier/diluent
F = formoterol
L_c = coarse particles of carrier/diluent
L_m = small particles of carrier/diluent produced by methods like micronisation, direct precipitation etc.
F_m = small particles of formoterol produced by methods like micronisation, direct precipitation etc.
B_m = small particles of glucocorticosteroid produced by methods like micronisation, direct precipitation etc.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01118

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/72, A61K 31/165, A61K 31/58, A61P 11/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6030604 A (JAN TROFAST), 29 February 2000 (29.02.00), the claims and column 3, lines 27-30	1-10
A	US 5795564 A (GUNNAR ABERG ET AL), 18 August 1998 (18.08.98)	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2001	04-10-2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01118

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01118

Claim 10 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/09/01

International application No.
PCT/SE 01/01118

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6030604 A	29/02/00	AU 731192 B	29/03/01
		AU 5785998 A	07/08/98
		BR 9811249 A	05/09/00
		CZ 9902557 A	13/10/99
		EE 9900295 A	15/02/00
		EP 1007017 A	14/06/00
		EP 1012576 A	28/06/00
		HU 0000714 A	28/08/00
		IL 130838 D	00/00/00
		JP 2000506967 T	06/06/00
		JP 2001508793 T	03/07/01
		NO 993539 A	20/09/99
		PL 334527 A	28/02/00
		SE 9700135 D	00/00/00
		SK 95999 A	18/01/00
		TR 9901690 T	00/00/00
		US 6147750 A	14/11/00
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US 5795564 A	18/08/98	US 6068833 A	30/05/00